

OFFICE OF GENERIC DRUGS

Review of Investigational New Drug Applications (Bio-INDs) by the Office of Generic Drugs

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PURPOSE

- This MAPP describes the Office of Generic Drugs (OGD) policy and procedures for review of investigational new drug applications (INDs) submitted for bioavailability or bioequivalence studies under 21 CFR 320.31. The term *Bio-INDs* distinguishes them from INDs for investigational new drugs submitted to the Office of New Drugs (OND). The Bio-IND is required by regulations in specific instances to ensure that proposed products that are not new drugs are safe for use in human test subjects and do not expose them to undue risk.
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BACKGROUND

- The requirements for submission of a Bio-IND in support of an abbreviated new drug application (ANDA) were revised when FDA published the Title I regulations in April of 1992. The revisions made the requirements for the submission of a Bio-IND consistent with the OGD practice at that time. The regulations state specifically when a Bio-IND must be submitted for an in vivo bioavailability or bioequivalence study in humans (21 CFR 320.31) and the required content of the IND (21 CFR part 312).
- As stated in 21 CFR 320.31(a), any sponsor planning to conduct an in vivo bioavailability or bioequivalence study in humans should submit a Bio-IND if:
 - (1) The study involves a radioactive labeled drug product, or
 - (2) The study involves a cytotoxic drug.
- As stated in 21 CFR 320.31(b), any sponsor planning to conduct a bioavailability study in humans using a drug product that contains an already approved, non-new chemical entity should

submit a Bio-IND if the study is one of the following types:

- (1) A single-dose study in normal subjects or patients where either the maximum single or total daily dose exceeds what is specified in the labeling of the drug product that is the subject of an approved new drug application (NDA) or an ANDA.
 - (2) A multiple-dose study in normal subjects or patients where either the single or total daily dose exceeds what is specified in the labeling of the drug product that is the subject of an approved NDA or ANDA.
 - (3) A multiple-dose study on a controlled-release drug product on which no single-dose study has been conducted.
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REFERENCES

- MAPP 6030.1 – IND Process and Review Procedures (Including Clinical Holds)
 - OGD Memorandum – “Operating Procedures for Handling INDs Within OGD,” May 6, 1996
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DEFINITION

- Clinical hold: An order issued by the FDA to the sponsor of an IND to delay or suspend a clinical investigation. It may be complete (i.e., to suspend all studies under the IND) or partial (i.e., to suspend only a portion of the study or studies).
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POLICY

- In addition to a bioequivalence study protocol, sufficient information should be available in a Bio-IND for OGD to determine the safety of the formulation to be used in the proposed bioequivalence study. For example, a qualitative and quantitative listing of all active and inactive ingredients should be provided. If an inactive ingredient exceeds the amount found in the Agency’s Inactive Ingredient Guide (IIG) (<http://www.fda.gov/cder/drug/iig>) or has not previously been used in a drug product intended for the same route of administration, OGD will request additional safety data from the applicant.
- OGD will determine whether complete information on chemistry, manufacturing, and controls has been included in a Bio-IND so that the safety of the planned study can be adequately evaluated. This material will need to be resubmitted with the ANDA.
- When FDA concludes there may be grounds for imposing a clinical hold, the Agency will attempt to discuss and satisfactorily resolve the matter with the sponsor before issuing the clinical hold order (21 CFR 312.42(c)).
- OGD’s Associate Director for Medical Affairs can discuss any safety related deficiencies identified in the proposed protocol with the applicant and suggest modifications to resolve safety concerns or place Bio-INDs on clinical hold (21 CFR 312.42).

RESPONSIBILITIES

- **The Document Room Staff will:**

Receive and identify a Bio-IND based on the cover letter and Form SF-1571.

Assign a control number in the 15,000 series and enter appropriate data into the IND management information system (MIS).

Create a charge and history card and enter all pertinent information into the IND logbook.

Route all three copies (original - red, duplicate - green, and triplicate - orange) to the IND coordinator.

Process outgoing clinical hold, deficiency, and other necessary action letters, and incorporate completed reviews into applications through OGD procedures.

Process incoming amendments, new correspondence, and periodic reports, and forward them to the IND coordinator.

- **The IND Coordinator will:**

Review new Bio-INDs for completeness and acceptability using the IND checklist (see Attachment A). Specific items that should be present include:

- Protocol for conducting an in vivo bioequivalence study in humans
- A qualitative and quantitative statement of the components and composition of the generic drug to be used in the bioequivalence study, including the amounts of the active ingredients and all excipients

Review any other information necessary to determine the safety of the formulation to be used in the proposed bioequivalence testing, including but not limited to the following items:

- Tests and specifications for identity, strength, quality, and purity for each active ingredient, and certificates of analysis for all excipients
- Method and place of manufacture, including a description of the type of equipment, batch size, and batch records
- Tests to be performed and specifications to be established for the finished dosage form (certificates of analysis)
- Stability testing data sufficient to demonstrate that the product is stable for the length of the study

Within 7 working days of the receipt of the investigational application, issue an acknowledgement letter by fax, and mail a copy of the letter to the sponsor.

Forward the green volume to the appropriate chemistry team leader, the orange volume to a project manager in the Division of Bioequivalence, and the red archival copy to the Document

Room.

After the acknowledgement letter is issued, inform the following individuals of the receipt of a Bio-IND and the projected response date:

Associate Director for Medical Affairs
Director, Division of Labeling and Program Support
Director, Division of Bioequivalence
Directors, Divisions of Chemistry I, II, and III
Team Leaders and Project Manager of Chemistry and Bioequivalence for the product to be studied

Monitor the chemistry and bioequivalence review processes to ensure that each review is complete within 25 days of the IND receipt date.

Identify and coordinate resolution of potential safety issues with the Associate Director for Medical Affairs.

Prepare the final deficiency letter, to include chemistry, bioequivalence, and medical comments, for the signature of the Director, Division of Bioequivalence.

If a secondary medical review is needed from an OND review division, prepare the consult, notify the OND project manager, identify the review as an IND review, and specify the date by which a response is needed.

If the reviewer in any discipline recommends a clinical hold, forward the recommendation of the reviewer and team leader to the Associate Director for Medical Affairs to assess the need for a clinical hold.

Ensure that a clinical hold letter is sent to the sponsor, if needed, detailing the reasons for the clinical hold and any other recommendations.

PROCEDURES

- The primary review (chemistry, bioequivalence, and medical, in addition to microbiological or statistical, as appropriate) will be completed expeditiously.
- If there are no deficiencies identified that would compromise patient safety, the study will be allowed to proceed.
- If a reason for a clinical hold is identified by any discipline, the potential for a hold will be communicated to the review team. The discipline team leader involved will concur or disagree with the recommendation of the reviewer.
- If the team leader agrees with the hold recommendation, the Associate Director for Medical Affairs will provide an assessment and make the final decision (including any input from secondary reviews from OND and the documentation from the review that is the basis for a

clinical hold).

- When the need for a clinical hold is identified (complete or partial):

The Associate Director for Medical Affairs or the Director of the Division of Bioequivalence will notify the sponsor representative by telephone of the need for a clinical hold. The reasons for the clinical hold will be discussed in detail. The telephone notification will be documented in the IND file, in the electronic file, and a copy will be sent to the Office Director and IND coordinator to inform them of the clinical hold.

A clinical hold letter will be prepared for the signature of the Office Director documenting the reasons for the clinical hold. It will be issued within 5 working days from the date the sponsor was notified of the clinical hold. Other recommendations identified in reviews that are not reasons for a clinical hold will be communicated as well. Such recommendations should be distinguished clearly from clinical hold deficiencies.

- On receipt and review by the discipline team leader, division director, and Associate Director for Medical Affairs of a satisfactory complete response from a sponsor, the clinical hold will be lifted. The firm will be notified by telephone, and a remove hold letter will be prepared for the signature of the Office Director.
- If it is determined that the clinical hold cannot be lifted, the sponsor will be notified by telephone and the call will be documented appropriately. As with the initial hold, the Office Director will be notified and a letter signed by the Office Director will be sent to the sponsor.

EFFECTIVE DATE

This MAPP is effective upon date of publication.

ATTACHMENT A

IND CHECKLIST FOR COMPLETENESS AND ACCEPTABILITY

IND # _____

DRUG NAME _____

DOSAGE FORM _____

CHEMISTRY TEAM _____

	YES	NO
Type of IND (Basis)		
FDA Form 1571 - Completed/Original Signature		
Table of Contents		
Introductory Statement		
General Investigational Plan		
Protocol		
Components & Composition		
Manufacturing Controls for Active Ingredient DMF		
Specification and Tests for Active Ingredient		
Source of Active Ingredient		
COA from Manufacturer of Active Ingredient		
Specification and Tests for Inactive Ingredients		
Source of Inactive Ingredients		
COA for Inactive Ingredients		
COA for Finished Dosage Form		
Manufacturing Controls (Method and Equipment)		
Address of Manufacturing Site		

Manufacturing Procedure (Batch Records) Batch/Lot #		
Stability Profile Including Stability Data		
3 Months Accelerated Stability Data		
Batch/Lot # Listed on Stability Records		
Container/Closure Information		
Environmental Assessment or Claim for Exclusion		
Compliance Statement		
Additional Information (Special Topics)		
Duplicate copy to HFD- ____ for consult. Type of consult: Date:		
Reviewing CSO _____ Date _____		
Recommendation: File Refuse to File		
Supervisory Concurrence _____ Date _____		

ATTACHMENT B
PROCESSING RECORD

IND # _____

APPLICANT _____

AIP: _____ YES _____ NO

DATE:

INITIALS:

REVIEW FOR ACCEPTABILITY

_____ DATE RECEIVED BY DOCUMENT ROOM

_____ DATE RECEIVED BY REGULATORY SUPPORT BRANCH

_____ DATE FORWARDED TO CSO/CSO TECH FOR REVIEW

_____ DATE FORWARDED FOR SUPERVISORY REVIEW

CHEMISTRY REVIEW

_____ DATE SENT TO CHEMISTRY TEAM LEADER

_____ DATE FORWARDED TO DIVISION DIRECTOR

BIOEQUIVALENCE REVIEW

_____ DATE SENT TO BIOEQUIVALENCE

_____ DATE FORWARDED TO DIVISION DIRECTOR

RECOMMENDATIONS